УДК 616.127-005.8:085.222.27:661.834:57.085.14
https://doi.org/10.20538/1682-0363-2024-3-66-73

Cardioprotective effect of lithium ascorbate in an *in vivo* model of myocardial infarction

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ABSTRACT

The aim of the work was to study the cardioprotective effect of lithium ascorbate in an *in vivo* model of myocardial infarction. In the course of the study, we searched for compounds promising for therapy of acute myocardial infarction.

Materials and methods. Myocardial infarction was modeled in Wistar rats by ligating the left coronary artery (the duration of ischemia was 45 minutes) followed by ligature loosening and 120-minute reperfusion. All manipulations were performed under alpha-chloralose anesthesia with mechanical lung ventilation and recording heart rate, blood pressure, and ECG. Lithium ascorbate was administered intravenously at a dose of 100 mg / ml before ischemia. The area at risk (the ischemia / reperfusion zone) was detected by staining the myocardium with tightened ligature with 5% potassium permanganate. After that consecutive myocardial slices were prepared, and infarct size was determined. Differentiation of the infarct size from the area at risk was performed by staining with 1% 2,3,5-triphenyl tetrazolium chloride solution for 30 minutes at 37 ºC. The infarct size and the area at risk were determined by the planimetric method. The serum concentration of myocardial damage marker creatine kinase-MB (CK-MB) was measured using ELISA kits.

Results. Lithium ascorbate reduced the infarct size / area at risk ratio by 38% and decreased the serum CPK-MB level in the experimental animals by 42% compared to the control group. Lithium ascorbate did not affect hemodynamics parameters during coronary artery occlusion and reperfusion.

Conclusion. The cardioprotective effect of lithium ascorbate in cardiac ischemia / reperfusion *in vivo* was found.

Keywords: myocardial infarction, lithium salts, ischemia, reperfusion, arrhythmias

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

Source of financing. The study was funded by the Priority 2030 program.

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Conformity with the principles of ethics. The study was approved by the Ethics Committee at Cardiology Research Institute of Tomsk NRMC (Protocol No. 207 of 23.12.2020).

For citation: Plotnikov E.V., Chernov V.I., Mukhomedzyanov A.V., Maslov L.N., Yusubov M.S., Larkina M.S., Artamonov A.A.6, Belousov M.V. Cardioprotective effect of lithium ascorbate in an in vivo model of myocardial infarction. *Bulletin of Siberian Medicine.* 2024;23(3):66–73. https://doi.org/10.20538/1682-0363-2024-3-66-73.

Кардиопротекторный эффект аскорбата лития на модели инфаркта миокарда *in vivo*

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РЕЗЮМЕ

Цель – изучение кардиопротекторного действия аскорбата лития на модели инфаркта миокарда *in vivo*. В ходе исследований проводился поиск соединений, перспективных для терапии острого инфаркта миокарда.

Материалы и методы. Моделирование инфаркта миокарда проводили на крысах линии Вистар массой 250–300 г путем наложения лигатуры на левую коронарную артерию (продолжительность ишемии 45 мин) с последующим ослаблением лигатуры и реперфузией продолжительностью 120 мин. Все манипуляции выполнялись под хлоралозным наркозом с искусственной вентиляцией легких и регистрацией частоты сердечных сокращений, артериального давления и электрокардиограммы. Аскорбат лития вводили в дозе 100 мг/мл перед ишемией внутривенно. Определяли зону риска (ЗР) – зону ишемии/реперфузии, для чего миокард с затянутой лигатурой окрашивали 5%-м перманганатом калия, после чего делали последовательные срезы миокарда и определяли зону инфаркта. Дифференцировку зоны некроза миокарда от ЗР осуществляли путем окрашивания 1%-м раствором 2,3,5-трифенил тетразолия хлорида в течение 30 мин при 37 ºС. Размер зоны инфаркта и зоны риска определяли планиметрическим методом. Концентрацию маркера повреждения миокарда креатинфосфокиназы-МВ (КФК-МВ) в сыворотке крови определяли иммуноферментным методом.

Результаты. Аскорбат лития статистически значимо уменьшал отношение зоны инфаркта к ЗР на 38% и снижал уровень КФК-МВ в сыворотке крови экспериментальных животных на 42% по сравнению с группой контроля. Аскорбат лития не повлиял на параметры гемодинамики на всех этапах развития коронароокклюзии и реперфузии.

Заключение. Установлено кардиопротекторное действие аскорбата лития при ишемии/реперфузии сердца *in vivo*.

Ключевые слова: инфаркт миокарда, соли лития, ишемия, реперфузия, аритмии

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Работа выполнена при поддержке программы «Приоритет 2030».

Соответствие принципам этики. Исследование одобрено этическим комитетом НИИ кардиологии Томского НИМЦ (протокол № 207 от 23.12.2020).

Для цитирования: Плотников Е.В., Чернов В.И., Мухомедзянов А.В., Маслов Л.Н., Юсубов М.С., Ларькина М.С., Артамонов А.А., Белоусов М.В. Кардиопротекторный эффект аскорбата лития на модели инфаркта миокарда *in vivo*. *Бюллетень сибирской медицины.* 2024;23(3):66–73. https://doi.org/10.20538/1682-0363-2024-3-66-73.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide. Despite the development of effective emergency care and primary prevention measures, CVD prevalence remains high [1]. In Russia, more than 50,000 people die from myocardial infarction each year, which accounts for more than 2.5% of all-cause mortality [2]. Among all CVDs, myocardial infarction remains the most common acute condition with high mortality. This fact indicates the relevance of developing new and more effective cardioprotective drugs.

Currently, the main approach in complex therapy of myocardial infarction is rapid myocardial reperfusion (surgical or pharmacological), which implies restoration of blood supply to ischemic heart tissue. A related approach is cardioprotection, which involves pharmacological protection of myocardial cells in cardiac ischemia and reperfusion. Broadly speaking, cardioprotection includes all drugs and agents that can preserve the pumping function of the heart, reduce infarct size, and prevent the occurrence of life-threatening arrhythmias by reducing or preventing myocardial damage.

Such drugs include compounds from different pharmacologic classes, including, for example, beta-blockers, which have a long history of use and clinically proven cardioprotective effects. The cardioprotective effect of opioid receptor agonists has been proven in a number of studies [3, 4]. However, many drugs have not proven to be effective in clinical trials [5]. The search for new cardioprotective agents continues due to the high relevance and demand.

At the same time, some compounds are not widely used in cardiology, despite their significant cardioprotective potential. Lithium salts can refer to this group. It was previously shown that lithium chloride has a neuroprotective effect and allows to reduce neuronal tissue damage in the zone of ischemic stroke [6–8]. It should be noted that lithium salts are widely used in psychiatry as mood stabilizers for the treatment of affective disorders, so the pharmacokinetics and toxicology of lithium are well known from clinical practice. However, the potential of these drugs is not limited to the treatment of mental disorders. In particular, the protective effect of lithium in ischemic conditions has been proven. In this regard, CVDs are the most promising target for lithium therapy. The development of this area requires the study of the mechanisms of action and the search for new applications of lithium salts.

The studies published to date allow to conclude that the anti-ischemic effect of lithium may be manifested not only in relation to the brain, but also in relation to other organs [9]. It is important to note that even though lithium has been used in medicine for almost a century, the mechanism of action of lithium salts in myocardial infarction has not been studied. Previously lithium has been shown to have cardioprotective effects on isolated myocardium [10]. Most of the described studies consider inorganic lithium salts, primarily chloride and carbonate. The therapeutic potential of lithium salts can be expanded by selecting an anionic component with antioxidant activity, which increases antioxidant properties of the salt and enhances cytoprotective properties in oxidative stress.

The aim of this work was to study the cardioprotective effect of lithium ascorbate in an *in vivo* model of myocardial infarction.

MATERIALS AND METHODS

All experiments were carried out in compliance with the principles of humanity set out in the Directives of the European Community (86/609/EEC) and the Declaration of Helsinki. The equipment of the Center for Collective Use “Medical Genomics” of Tomsk NRMC was used in the work.

Lithium ascorbate was used as a test preparation. For these experiments, lithium ascorbate was obtained *ex tempore* by reaction between ascorbic acid and lithium carbonate (ACS reagents, Sigma-Aldrich) according to the described method [11]. The white powder was obtained, which was tested for authenticity using infrared (IR) spectrometry and elemental analysis. Lithium ascorbate was dissolved in normal saline and injected intravenously during the experiment.

Wistar rats weighing 250–300 g were used as experimental animals. The animals were kept in standard conditions, with natural day and night regimen and unlimited access to food and water. Before performing the experimental procedures, the animals were randomly distributed into two groups of eight rats each (control and experimental group). In the experimental group, the drug was injected into the femoral vein at a concentration of 100 mg / ml in 1 ml of normal saline 10 minutes before ischemia. A similar volume of saline solution was injected into the femoral vein in the control group 10 minutes before ischemia.

Solution of α-chloralose (Sigma) was used for anesthesia during surgical modeling of myocardial infarction (intraperitoneal injection at a dose of 60 mg / kg). Anesthetized animals were then connected to the SAR-830 Series mechanical ventilation system (CWE Inc., USA). Heart rate (HR) and blood pressure (BP) were measured using the SS13L pressure sensor (Biopac System Inc., Goleta, USA). The sensor was connected to the MP35 data acquisition system (Biopac System Inc., Goleta, USA). Electrocardiography was also performed on this device; ECG was recorded automatically throughout the experiment. Direct surgery on the heart was carried out according to the method of J.E. Schultz et al. [12].

Ligation of the left coronary artery was performed, which resulted in controlled ischemia in its basin. After 45 minutes of ischemia, the ligature was removed and blood flow restoration was confirmed by the emergence of hypraemia. The reperfusion period lasted 120 minutes. The detection of the necrotic zone and myocardial area at risk was performed according to the method described in the study by J. Neckar et al. [13]. To do this, after completion of the reperfusion period, the heart was removed followed by retrograde flushing. The heart was flushed with normal saline through the aorta.

The area at risk, i.e. the myocardial area subject to ischemia – reperfusion injury, was identified as follows. The ligature applied for ischaemia was re-ligated, and the cardiac muscle tissue was stained through the aorta with 5% potassium permanganate solution. After flushing the heart with normal saline, it was frozen and sliced perpendicular to the longitudinal axis in 1-mm-thick slices using the HSRA001-1 precision slicer (Zivic Instruments, Pittsburgh, USA) according to standard histologic techniques.

Visual differentiation of the necrotic zone (NZ) from the area at risk (AAR) was performed by treating with a 1% solution of 2,3,5-triphenyl tetrazolium chloride for half an hour in the thermostat at 37 ºC. During this process, oxidized 2,3,5-triphenyl tetrazolium chloride is reduced under the effect of dehydrogenases, which is manifested by the emergence of permanent staining. Active dehydrogenases were absent in the zone of heart muscle necrosis, and, consequently, this zone was not stained. At the end of treatment, all slices were fixed with 10% formalin for 24 hours. The obtained myocardial tissue samples were scanned from different sides using the HP Scanjet G4050 scanner. The sizes of AAR and NZ were determined by the planimetric method. The infarct size was expressed as a percentage of the hypoperfusion zone (AAR) as the NZ / AAR ratio. The activity of CPK-MB was determined using ELISA kits (Cloud-Clone Corp, Wuhan, China). CPK-MB in blood serum was determined using the Infinite 200 PRO microplate reader (Tecan GmbH, Austria).

Statistical analysis of the data was performed using specialized GraphPad Prism 9 (GraphPad Software, CA, USA) and MS Excel (Microsoft, USA) software. The results were shown as the mean and the standard deviation ($M \pm m$). The statisctical significance of the differences between the groups were identified using the Mann – Whitney test. The differences were considered significant at $p < 0.05$.

RESULTS

The assessment of HR dynamics at various stages of infarction modeling with lithium is shown in Figure 1. The assessment of BP dynamics at various stages of infarction modeling when exposed to lithium is presented in Figure 2. The results of the evaluation of lithium cardioprotective effect parameters on the myocardial infarction model are presented in Tables 1 and 2. The evaluation of heart rhythm disturbances during ischemia – reperfusion injury is shown in Table 3.

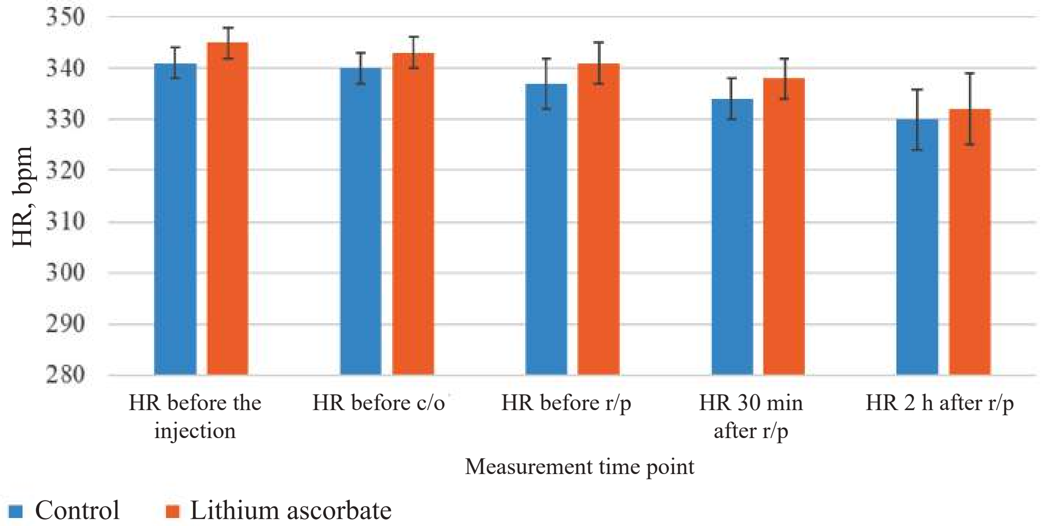

Fig. 1. Heart rate (HR) assessment in the animals at different time points during the experiment, bpm; c/o – coronary occlusion (45 minutes); r/p – reperfusion (120 minutes).

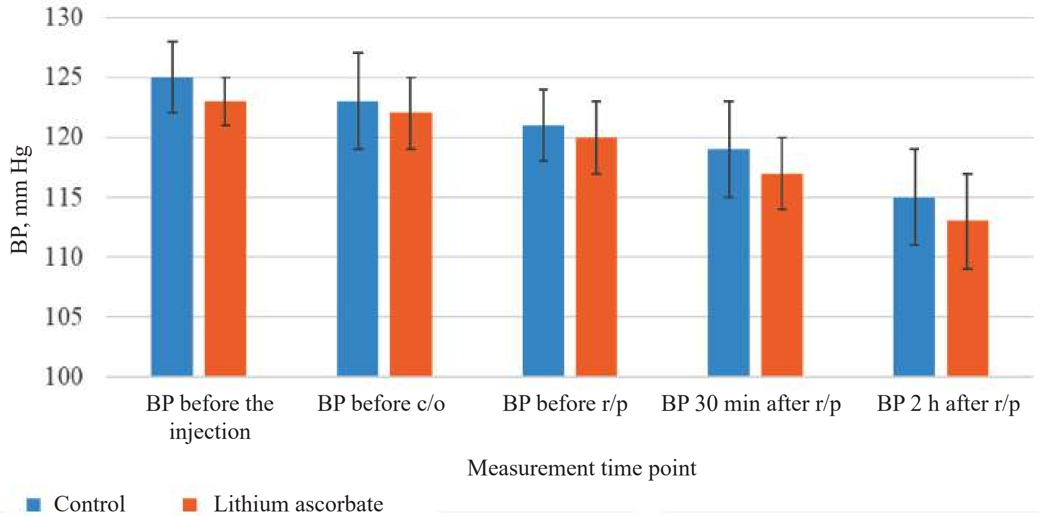

Fig. 2. Blood pressure (BP) assessment in the animals at different time points during the experiment, mm Hg; c/o – coronary occlusion (45 minutes); r/p – reperfusion (120 minutes).

Table 1

Calculated sizes and parameters of myocardial infarction area (45-minute ischemia, 120-minute reperfusion) in experimental animals, *M* ± *m*

Group	Necrotic zone, mg	Area at risk, mg	NZ / AAR, %	Right ventricular mass, mg	Left ventricular mass, mg
Control, *n* = 8	271 ± 52	561 ± 101	48 ± 3	187 ± 12	988 ± 11
Lithium ascorbate, *n* = 8	119 ± 32*	394 ± 95	30 ± 2*	181 ± 10	± 11

* statistically significant difference from the control group, $p < 0.05$ (here and in Table 2)

Table 2

Creatine phosphokinase-MB concentration in the blood serum of rats with modeled myocardial infarction (45-minute coronary occlusion, 120-minute reperfusion), $M \pm m$

Group	Serum CPK-MB concentration, U / l
Control, n = 8	104.3 ± 13.2
Lithium ascorbate, n = 8	60.5 ± 10.4*

Table 3

Frequency and types of arrhythmias in the rats with modeled myocardial infarction at the stage of ischemia (45-min coronary occlusion), %

Group	Ischemia (45 min)			
	Without arrhythmias	Multiple ventricular extrasystoles	Ventricular tachycardia	Ventricular fibrillation
Control, n = 8	0	100	87.5	25
Lithium ascorbate, n = 8	12.5	87.5	62.5	12.5

Note. Data are shown as a percentage from the corresponding animal group.

DISCUSSION

The experimental drug was administered to the animals intravenously at a dose of 100 mg / ml in normal saline in a volume of 1 ml 10 minutes before the onset of ischemia. The control group received intravenously normal saline in the same volume, and no significant changes in hemodynamics were observed immediately after administration (Fig. 1, 2). Lithium ascorbate did not affect HR (Fig. 1) and BP values (Fig. 2) at all stages of the ischemia development. During the development of ischemia, a slight trend toward a decrease in BP and HR was noted. However, even at the final stage of reperfusion, these parameters did not significantly differ from the baseline values in the animals.

The assessment of myocardial ischemic damage under lithium ascorbate exposure showed a decrease in cardiomyocyte death, which was expressed in a significant decrease in the NZ / AAR ratio by 38% compared to the control group (Table 1). The decrease in this parameter reflects greater myocardial preservation in AAR and a proportional decrease in the zone of ischemic heart injury during lithium exposure. Significant reduction of myocardial damage is confirmed by the biochemical analysis of serum CPK-MB level in the experimental animals (Table 2). We detected a decrease in the CPK-MB level in myocardial infarction under lithium exposure by 42% compared to the control group (blood was taken at the final stage after coronary occlusion and reperfusion).

Thus, it can be concluded that lithium administration before ischemia is accompanied by a pronounced cardioprotective effect, manifested by a decrease in the infarct size and serum concentration of CPK-MB, a myocardial cell damage marker. At the same time, lithium ascorbate administration was not accompanied by hemodynamic deterioration at the stages of coronary occlusion and reperfusion in the experimental animals. During all manipulations, HR was monitored, which is an important parameter in assessing the cardioprotector effectiveness. In this context, it is important to note that in clinical practice, life-threatening ventricular arrhythmias are a severe complication usually accompanied by a decrease in myocardial contractility [14]. The occurrence of such arrhythmias adversely affects the prognosis in patients with myocardial infarction and often leads to death [15].

In this study, various arrhythmias, including multiple ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation, were identified in the control group (Table 3). The identified arrhythmias were generally reversible and sinus rhythm was restored and, in some cases, transitioned to another cardiac rhythm disturbance, so there could be more than one type of arrhythmia in one animal. After 45-minute ischemia, no arrhythmias occurred in all experimental groups, so the antiarrhythmic effect was assessed only during ischemia. The group which received lithium ascorbate showed a decrease in arrhythmias of all types, including ventricular fibrillation that is the most critical one, but no statistically significant differences were found compared to the controls during this experiment (Table 3).

The presented results are consistent with the literature data obtained on isolated organs [16]. Several most probable mechanisms of lithium effect during ischemia explain the cardioprotective effect of lithium, including competitive antagonism to the main biological ions (Na, K), induction of nitric oxide synthesis, and influence on protein kinases and related metabolic pathways. These pathways are known to be involved in the realization of the cardioprotective effects of opioids [17]. It has been previously shown that the effect on ATP-sensitive potassium channels (KATP channels) plays an essential role in cardioprotection and pathological process in myocardial infarction [18]. As a target of lithium, these channels are protein structures whose activity is regulated by intracellular nucleotides. They act mainly in muscles and neurons, where, under conditions of energy shortage in the form of ATP, they can reduce cell excitability, which contributes to its survival under stressful conditions. It is important to note that lithium can exert multiple effects on a number of targets simultaneously in different tissues [*9*]. The results obtained imply further study of the cardioprotective effect of lithium salts.

CONCLUSION

The results of the study revealed an infarct size-limiting effect of lithium ascorbate with no significant effect on hemodynamics. During the experiment, we detected a decrease in myocardial NZ by 38% and a fall in the serum CPK-MB level by 42% compared to the control group.

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Authors' contribution

Plotnikov E.V. – conception and design, carrying out of research, drafting of the manuscript. Chernov V.I. – analysis of the data, substantial intellectual contribution, drafting of the manuscript. Mukhomedzyanov A.V. – performing operations in vivo, drafting of the manuscript. Maslov L.N. – conception and design of the in vivo study, interpretation of the results, drafting of the manuscript. Yusubov M.S. – analysis of lithium compounds, processing of the results, substantial intellectual contribution, drafting of the manuscript. Larkina M.S. – chemical synthesis, drafting of the manuscript. Artamonov A.A. – statistical processing of the results, graphic design, drafting of the manuscript. Belousov M.V. – analysis of the research results, drafting of the manuscript. All the authors approved the final version of the article.

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Received 04.03.2024;
approved after peer review 13.05.2024;
accepted 23.05.2024